

### Remarks and Arguments

Claims 1, 4-8 and 11-19 were presented for examination. Claim 1 has been amended.

Claims 1, 4, 7, 8 and 11 have been rejected under 35 U.S.C. §103(a) as obvious over articles entitled "Metal Nanoparticle-Based Electrochemical Stripping Potentiometric Detection of DNA Hybridization", J. Wang et al., *Analytical Chemistry*, 1999, 73(22), 5576-5581 (Wang et al., previously cited), "Potentiometric stripping analysis and anodic stripping voltammetry for measurement of copper(II) and lead(II) complexation by fulvic acid: A comparative study", R.M. Town, *Electroanalysis*, 1997, 9(5), 407-415 (Town) and U.S. Patent No. 5,292,423 (Wang) in view of PCT Patent Publication WO 1999/27367 A1 (Knoll, previously cited). The examiner comments that Wang et al. teaches all of the elements in claim 1 and asserts that, while Wang et al. does not explicitly mention use of an electrolyte and formation of a galvanic element, such elements are inherent to the Potentiometric Stripping Analysis (PSA) method taught in Wang et al. as evidenced by Town and Wang.

In his comments regarding the Wang et al. reference, it is clear that the examiner is interpreting the PSA method as being equivalent to a method for forming a galvanic cell. Applicants believe that this equivalence is not correct. In particular, Figure 1 of the Wang et al. reference shows a schematic representation of the analytical protocol. This protocol includes: (1) immobilizing probe molecules on beads, (2) hybridizing analyte molecules with gold nanoparticles to the probe molecules, (3) dissolving the gold nanoparticles, (4) depositing dissolved gold onto a working electrode, (5) stripping the deposited gold from the working electrode either chemically or electrochemically, and (6) monitoring the change of potential of the working electrode over time during the stripping process.

Steps (4) to (6) are inherent to a PSA analysis. A description of PSA can be found in the attached document entitled "Terminology and Convention for Electrochemical Stripping Analysis", A. Fogg and J. Wang, *Pure Applied Chemistry*, 1999, 71, 891- 897, relevant portions underlined). During the deposition step (4), a potential is necessarily applied to the working electrode (see, for example, Town, column 1, "The deposition step in PSA is identical to that in the anodic stripping

techniques, viz a constant potential is applied to the working electrode for fixed time during which metal ions in solution are reduced to their elemental state and amalgamate with (and are concentrated at) the mercury electrode." Stripping in step (6) is actively carried out by adding chemical reductants at fixed concentrations or by applying a constant current. The transition time of the potential signal is related to the amount of gold deposited on the electrode (see: Fogg and Wang).

The process set forth in Wang et al., Town and Wang cannot form a galvanic cell as recited in amended claim 1, lines 14-16: "...the counterelectrode and the metal surfaces of the nanoparticles form electrodes of a galvanic cell..." There are several reasons for this conclusion. First, during a PSA process, the nanoparticles are dissolved. Therefore, they cannot form one electrode of a galvanic cell. Second, as is well-known, in a galvanic cell, oxidation and reduction take place at electrodes in two spatially-separated half cells, whereas in a PSA process, both reactions take place at the working electrode. Thus, the working electrode cannot form an electrode of a galvanic cell as recited in claim 1.

Third, if the two half cells of a galvanic cell are not electrically connected, a substantially constant potential difference is generated between galvanic cell electrodes. Even if the two electrodes are connected, the potential difference remains constant and will not drop until the electrode of the less-noble element or the electrolyte at the electrode of the more-noble element is completely consumed. In a PSA process a transient potential signal is measured, not "...one of a substantially constant current and a substantially constant voltage generated between the electrodes of the galvanic cell..." as recited in amended claim 1, lines 17-19.

Therefore, amended claim 1 patentably distinguishes over the PSA process disclosed in Wang et al., Town and Wang which references do not disclose the recited galvanic cell. The Knoll reference has been previously discussed where it was pointed out that, in the Knoll reference, nanoparticles are electrically isolated and do not form one of the electrodes of a galvanic cell. Thus, the combination of Wang et al., Town and Wang with Knoll does not teach or suggest the elements recited in amended claim 1.

Claims 4, 7, 8 and 11 depend, either directly or indirectly on amended claim 1, and incorporate the limitations thereof. Therefore, these latter claims also patentably distinguish over the cited reference combination in the same manner as amended claim 1. In addition, these claims also recite limitations not disclosed or suggested by the cited combination of references. For example, claim 11 recites that electrical contact between the nanoparticles and the contact spot is established by electrically conductive molecules. The examiner points to Knoll, which indicates that the disclosed marker particles are conductive. However, in Knoll the marker particles correspond to the nanoparticles of the present invention. Thus, in Knoll, there are no additional electrically conductive molecules as recited in claim 11.

Claims 6, 18 and 19 have again been rejected under 35 U.S.C. §103(a) as obvious over Wang et al, Town, Wang and Knoll in view of U.S. Patent No. 6,391,558 (Henkens, previously cited.) The examiner comments that the Wang et al, Town, Wang and Knoll references disclose all of the claimed limitations with the exception that they do not explicitly disclose covalent binding for immobilizing the probe molecules as recited in claim 6 or PCR amplification as recited in claims 18 and 19. However, the examiner claims that the Henkens reference discloses both covalent binding and PCR techniques in conjunction with detection of nucleic acids using electrodes with immobilized probes.

As previously discussed, the Henkens reference discloses measuring the presence and quantity of "reporter" particles by a technique in which current pulses are applied to a working electrode on which the probe molecules have been immobilized and to a reference electrode. The responses of each electrode are monitored to determine the quantity of reporter particles present. Henkens does not disclose the formation of a galvanic cell that, in turn, generates an output, which can be measured, as now recited in claim 1 on which claims 6, 18 and 19 depend. Thus, neither the Wang et al, Town, Wang and Knoll references nor the Henkens reference discloses the construction of such a galvanic cell.

Claims 5 and 12 have been rejected under 35 U.S.C. §103(a) as obvious over Wang et al, Town, Wang and Knoll in view of U.S. Patent No. 6,207,369 (Wohlstädter, previously cited.) The examiner comments that Wang et al, Town, Wang and Knoll

disclose the recited limitations with the exception that they do not disclose the use of polyene molecules to conduct electrical signals as recited in claims 5 and 12. However, the examiner indicates that Wohlstadter discloses such a use of a linking chain in the polyene class to insure low resistance transfer of electrons from an electrode.

As discussed above, the Wang et al, Town, Wang and Knoll references do not teach the formation of a galvanic cell as claimed in claim 1, the parent claim of claims 5 and 12. Adding Wohlstadter to this combination does not change this conclusion because Wohlstadter detects the presence and quantity of the analyte molecules by electrochemiluminescence, not by forming a galvanic cell and then measuring the electrical properties of that element as recited.

Claims 13, 16 and 17 have been rejected under 35 U.S.C. §103(a) as obvious over Wang et al, Town, Wang and Knoll in view of PCT Patent Publication No. WO 02/054052 A1 (Fish, previously cited.) The examiner comments that Wang et al, Town, Wang and Knoll disclose the recited limitations with the exception that they do not disclose moving a countersurface to press nanoparticles against a contact spot, but the examiner indicates that Fish discloses the detection of analyte molecules with an electrode-based scheme in which an opposing surface with an electrode is moved to make contact with an electrically-readable particle.

The Fish reference has been discussed in detail in the previous response mentioned above. Combining Fish with Wang et al, Town, Wang and Knoll would not produce an arrangement which forms a galvanic cell and measures the voltage or current across the electrodes of this element because Wang et al, Town, Wang and Knoll do not disclose the recited galvanic cell and Fish detects the presence and quantity of the analyte molecules by measuring electrical changes in a measuring cell, not by forming a galvanic cell and then measuring the electrical properties of that element as recited. Since claims 13, 16 and 17 are dependent on amended claim 1 and incorporate the limitations thereof, they distinguish over the cited reference combination in the same manner as claim 1.

Claims 14 and 15 have been rejected under 35 U.S.C. §103(a) as obvious over Wang et al, Town, Wang and Knoll in view of Fish and further in view of Wohlstadter. The examiner comments that Wang et al, Town, Wang, Knoll and Fish disclose the

recited limitations with the exception that they do not disclose that the analyte is collected on a surface opposite to the surface on which the detecting electrode is mounted. The examiner indicates that Wohlstadter discloses several electrode-based detection configurations in which an analyte is collected on a surface opposite to the surface on which the detecting electrode is mounted.

The combination of Wang et al., Town, Wang, Knoll and Fish has been discussed above and does not teach the formation of a galvanic cell as claimed. Adding Wohlstadter to this combination does not change this conclusion because Wohlstadter detects the presence and quantity of the analyte molecules by electrochemiluminescence, not by forming a galvanic cell and then measuring the electrical properties of that element as recited. Since claim 14 is dependent on amended claim 1 and incorporates the limitations thereof, it distinguishes over the cited reference combination in the same manner as claim 1.

In light of the forgoing amendments and remarks, this application is now believed in condition for allowance and a notice of allowance is earnestly solicited. If the examiner has any further questions regarding this amendment, he is invited to call applicants' attorney at the number listed below. The examiner is hereby authorized to charge any fees or direct any payment under 37 C.F.R. §§1.17, 1.16 to Deposit Account number 50-3969.

Respectfully submitted

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/paul e. kudirka/ Date: 2008-01-17  
Paul E. Kudirka, Esq. Reg. No. 26,931  
LAW OFFICES OF PAUL E. KUDIRKA  
Customer Number 64967  
Tel: (617) 357-0010 Fax: (617) 357-0035